Neuroscience and Biobehavioral Reviews 47 (2014) 656–669

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Can sleep apnea cause Alzheimer's disease?

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form 17 August 2014
Accepted 22 October 2014
Available online 30 October 2014

Keywords:
Sleep apnea
Alzheimer's disease
Sleep fragmentation
Hypoxia
Oxidative stress
Autophagy

ABSTRACT

Both obstructive sleep apnea (OSA) and Alzheimer's disease (AD) are increasing health concerns. The objective of this study is to review systematically the effects of OSA on the development of AD. The search was conducted in PubMed and Cochrane CENTRAL, and followed by a manual search of references of published studies. Cross-sectional, cohorts, and randomized clinical trials were reviewed. Besides clinical studies, we also discuss neuroimaging data, experimental animal evidence, and molecular mechanisms. Although a causal relationship between OSA and AD is not yet established, OSA induces neurodegenerative changes as a result of two major contributing processes: sleep fragmentation and intermittent hypoxia. As such, inflammation and cellular stress are sufficient to impair cell–cell interactions, synaptic function, and neural circuitry, leading to a decline of cognitive behavior. Sustained OSA could promote cognitive dysfunction, overlapping with that in AD and other neurodegenerative diseases. Early treatment by positive airway pressure and other current standards of care should have a positive impact to alleviate structural and functional deterioration. With better understanding of the cellular and neurophysiological mechanisms by which OSA contributes to AD, we may identify novel molecular targets for intervention.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2014.10.019
0149-7634/

1. Introduction

A growing body of the literature has identified a critical link between sleep and health. With modern life styles, more people are sleeping less than their biological needs (Bixler, 2009; Krueger and Friedman, 2009; Knutson et al., 2010). Inadequate sleep, reduced physical activity, and increased caloric intake all contribute to the development of obesity and obstructive sleep apnea (OSA). Severe OSA further induces sleep fragmentation, intermittent hypoxia, and oxidative stress during reoxygenation. In this context, we discuss how sleep disorders interfere with daily functions and impair cognitive reserve. This is pertinent to the evaluation and treatment of mild cognitive impairment (MCI) and dementia (vascular, Alzheimer's, and other forms of neurodegeneration).

OSA is a prevalent medical problem with a high socioeconomic burden (Committee on Sleep Medicine and Research Board on Health Sciences Policy, 2006). It affects a high percent of the elderly population as discussed below, though a 1996 UK study estimated a minimal prevalence of 5.7% in men and 1.2% in women at 35–69 years of age (Davies and Stradling, 1996). Polysomnography (PSG) remains the gold standard for diagnosis. To establish a diagnosis of OSA based on criteria from the American Academy of Sleep Medicine, patients typically have an apnea-hypopnea index (AHI) $\geq$5 events/h on PSG in association with symptoms of impaired daytime function, or $\geq$15 events/h when asymptomatic. Besides AHI, the extent and duration of intermittent hypoxia and the severity of impairment of sleep architecture also predict daytime dysfunction and medical complications. Sleep disordered breathing (SDB) is a more generalized term, including habitual snorers not yet fitting into the diagnostic criteria of OSA. The rate of undiagnosed cases is high, estimated to involve 82% of men and 93% of women (Daulatzai, 2013). Does OSA cause a subset of Alzheimer's disease (AD) and other forms of neurodegeneration? If so, does treatment of OSA prevent AD progression? Here, we address the link between OSA and AD by performing systematic reviews of clinical studies. We also discuss relevant neuroimaging findings as well as experimental results from animal and cellular research. Some of the key issues are: differentiation of cognitive functional domains primarily affected in OSA patients and AD patients; structural correlates; and potential reversibility by treating OSA.

2. Systematic review of clinical studies

2.1. Data sources and searches

Following guidelines specified in the Cochrane Handbook (Higgins and Green, 2011) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al., 2009), we searched PubMed and Cochrane CENTRAL. The following medical subject headings (MeSH) and key words were used: "Sleep apnea" (or "sleep apnoea") and "Alzheimer's disease". The duration of the search starts from the beginning of each database till the beginning of 2014, the time of submission of this review.

2.2. Data extraction and analysis

Duplicated entries in different databases were scrutinized. This was followed by a manual search of references of published studies. Inclusive criteria encompassed studies describing general data (study design), patients (number of included patients, mean age, gender), type of diagnostic criteria and/or intervention strategy used, and timing of determination, with full text English language publication available for evaluation. Besides original research listed in the tables, some pertinent reviews with new information were also covered in the text, as they were particularly helpful in identifying original studies not covered in the original search. Studies of most non-AD causes of neurodegeneration were excluded, with the exception of discussion of some Parkinson's disease and vascular (multi-infarct) dementia studies, as they show substantial overlap with AD.

The validity of statistical association between OSA and AD was assessed by evaluation of alternative explanations from chance, bias, and confounding influences. Potential causal effects were determined by positive criteria of the strength of association, totality of evidence, biological credibility, and dose-response or threshold effect. The generalizability is discussed in regard to the features of the study population. Risk of bias was assessed for allocation, blinding, incomplete outcome, selective reporting, comparable treatment groups, and other sources that might increase the risk of bias, such as carry-over effects in crossover designs or conflicts of interest.

2.3. Results

The electronic search to January 2014 resulted in a total of 50 results on PubMed, and no pertinent new ones on Cochrane CENTRAL. There were 19 full text articles meeting eligibility criteria and these were obtained. Additional records were identified by cross-checking the reference lists and updated search at the time of revision of this review manuscript in July 2014. We reviewed studies about three major issues: (1) the prevalence and distribution of sleep disorders in the elderly; (2) in people with OSA, whether there is an increased incidence of AD or other types of dementia, and whether there is a potential association between OSA and AD; and (3) whether treatment improves cognitive dysfunction in OSA patients.

2.4. A priori 1: Increased incidence of sleep disordered breathing with age

Self-report questionnaire and sleep diagnostic findings can be quite different, even in the same population. The initial estimate of 2905 Japanese-American men (71–93 year old) in the Honolulu-Asia Aging Study showed a 2% incidence of apnea and 8% of daytime sleepiness (Foley et al., 1999). Portable sleep studies showed that the incidence of SDB reached 70% in people older than 80 and the incidence of severe OSA (AHI $\geq$30 events/h) was 19% (Foley et al., 2003).

There are also differences among different populations across time and space. Among the 5201 participants from the Cardiovascular Health Study (65 years and older), 33% men and 19% woman reported loud snoring. Observed apnea was seen in 13% of men and 4% of women (Enright et al., 1996). This estimate is higher than the questionnaires in the Honolulu-Asia Aging study mentioned above (Foley et al., 1999). The sensitivity and specificity of self-reported snoring have been assessed in patients 60 years or older in a sleep clinic; men showed 65% sensitivity and 72% specificity, whereas women had 61% sensitivity and 81% specificity (Bliwise et al., 1991). PSG remains the gold standard for diagnosis.

In a full spectrum that encompasses SDB, sleep problems are common in the elderly. In demented patients, the incidence of sleep disturbance reached 71%, whereas the non-demented controls showed a lower rate of 55.7% (Rongve et al., 2010). In asymptomatic elderly, the presence of moderate to severe OSA was seen in 53 subjects among the 151 Norwegians sampled, whereas white matter changes were present in 199 patients. Even after adjustment for hypertension, there was a significant association between OSA and white matter change (Kim et al., 2013).

2.5. A priori 2: Increased incidence of sleep apnea and all causes of sleep disorders in neurological diseases in the elderly

The prevalence of SDB (mainly OSA) increases with that of neurological disorders. SDB predicts a poorer functional prognosis in stroke patients at 3 and 12 months after the acute event, with a higher mortality. SDB is more frequent in AD than non-demented older subjects, and its severity correlates with cognitive impairment (Janssens et al., 2000). This indicates a reciprocal relationship between SDB and neurological dysfunction.

In regard to comorbidity of sleep disorders with neurological diseases, questionnaires estimate that patients with vascular dementia show a higher frequency of OSA. Although this study showed that AD and MCI have the same frequency of any sleep disorder (Guarnieri et al., 2012), a French review in 2010 estimated the age-dependent increase of OSA to be 25% in older adults and up to 48% in patients with AD. The cognitive dysfunction was ascribed to reduced cerebral blood flow (CBF), ischemic brain lesions, microvascular reactivity, white matter lesions, and gray matter loss. The changes involved many cognitive domains, including attention, executive functioning, motor efficiency, working memory, and long-term episodic memory. This led to the proposal that CPAP therapy might improve cognitive functioning in these patients (Onen and Onen, 2010).

AD patients tend to have more severe sleep disorders (Bombois et al., 2010). Regarding whether OSA patients have a higher incidence of AD, stratified analysis is often necessary to find differences in subpopulations. There are more female SDB patients developing AD (Reynolds III et al., 1985), but men tend to have higher AHI and have a greater association of OSA with multi-infarct dementia rather than AD (Erkinjuntti et al., 1987). Elderly men are more likely to show co-existing OSA and AD (Smallwood et al., 1983). Intriguingly, AD patients show more NREM-predominant than REM-related apnea (Hoch et al., 1986). This suggests altered neurophysiological mechanisms of sleep breathing control involving chemoreflex sensitivity and ventilation control.

2.6. Cross-sectional studies addressing the association between OSA and AD (Table 1)

Table 1 lists cross-sectional studies first by chronological order, then alphabetically by the last name of the first author. Several recent studies explored specific cognitive domains influenced by the severity of sleep apnea. Elderly patients with OSA showed greater impairment in delayed recall than age-matched non-OSA controls, contributed to by oxygen desaturation index and education level (Ju et al., 2012). Conversely, impaired language function in MCI patients was related to poor sleep quality and more severe OSA (Kim et al., 2011).

In a 1995 study of 17 sleep apnea patients compared with 17 normal controls, focused frontal lobe-related tests addressed attention, short-term memory spans, learning abilities, planning and programming capacities, categorizing activities and verbal fluency. Patients with sleep apnea were less able to initiate new mental processes and to inhibit automatic ones, and showed a tendency for perseverative errors. Verbal and visual learning, as well as memory spans, were also decreased. It appears that the AHI was related to memory deficits whereas the level of nocturnal hypoxemia contributed to typical frontal lobe-related abnormalities (Naegele et al., 1995).

There also are studies showing elderly subjects with impaired cerebral oxygen reserve and cognitive function in the absence of OSA. There was a correlation between cognitive function and awake resting cerebral oxyhemoglobin saturation and its reduction during sleep (Carlson et al., 2011). This is consistent with the multifactorial nature of MCI and dementia.

2.7. Cohort studies (Table 2)

Table 2 lists population-based longitudinal studies, mainly follow-up of OSA patients on hazardous ratio (HR) to develop cognitive dysfunction. By comparison of the incidence of cognitive decline between patients with and without OSA, the data would provide more reliable risk estimates than cross-sectional observational studies of the association.

A 2011 paper shows that the incidence of SDB in elderly women (AHI $\geq$15 events/h on PSG) reaches 35% and an adjusted odds ratio to develop MCI or dementia is 1.85. The extent of hypoxemia has a greater impact than sleep time or severity of sleep fragmentation (Yaffe et al., 2011). The result is consistent with a large scale cohort study in Taiwan, which determined 5-year dementia-free survival rates in OSA patients. The development of dementia was more probable in the first 2.5 years of follow-up. The hazard ratio was 1.7 overall and 2.38 for women. Males in the 50's had 6.08 times greater risk, whereas females at age 70 or older had 3.20 times greater risk of developing dementia. The gender, age, and time-dependent effect supports a potential causal relationship of OSA leading to dementia (Chang et al., 2013).

2.8. Randomized double-blind placebo-controlled trials (Table 3)

The immediate effect of CPAP on mental concentration is apparently related to the improvement of sleep quality and resolution of excessive daytime sleepiness. To address reversibility of memory deficit and other cognitive domains affected by OSA, several small size randomized double-blind placebo-controlled trials determined the effect of CPAP treatment. In an excellent review by Matthews and Aloia in 2011, 16 studies were summarized (Matthews and Aloia, 2011). Most of them are not reiterated here. From data shown in Table 3, it appears that 6 weeks of CPAP not only improves sleep architecture, but also improves cognition. Even 3 weeks of treatment followed by another 3 weeks of placebo CPAP showed a sustained effect. The cognitive domains affected were episodic verbal learning and memory, and some aspects of executive functioning such as cognitive flexibility and mental processing speed (Ancoli-Israel et al., 2008). One-year follow up of 5 patients suggests that persistent CPAP users have less cognitive decline, depression, or excessive daytime sleepiness. Subjective sleep quality was improved in both patients and caregivers (Cooke et al., 2009b). With the same design in 39 AD patients, therapeutic CPAP use decreased Epworth sleepiness scale (ESS) after 3 weeks, indicating a reduction of excessive daytime sleepiness (Chong et al., 2006).

In contrast to a beneficial effect of OSA treatment to enhance cognitive functions, management of AD also reduces excessive daytime hypersomnolence. In a small randomized, double-blind, placebo-controlled study in Brazil, donepezil improved AHI, desaturation index, duration and extent of hypoxemia, suggesting that the cholinesterase inhibitor improves subjective measures of OSA. Independently, it also increased REM sleep duration and reduced ADAS-cog scores (Moraes et al., 2008). Despite a decrease of sleep efficiency, there was a reduction of ESS scores. The findings suggest that enhanced cholinergic transmission improves OSA (Sukys-Claudino et al., 2012).

2.9. Overall strengths and limitations of the existing data

The current literature undoubtedly shows an increased incidence of OSA in the elderly. OSA is associated with a higher incidence of dementia in most, but not all studies. Besides AD, vascular dementia may also show a positive correlation with OSA. To maintain a focus of this review, we do not cover Parkinson's disease, Lewy body dementia, and many aspects of parasomnia in this

Table 1
Cross-sectioning studies.

Author	Country and samples	Age (y)	OSA: ascertainment of cases	AD: N of cases and diagnostic criteria	Results	Covariants	Comment on positive criteria	Comment on risk of bias
Smallwood et al. (1983)	US, 5 groups; 10 young male 24 elderly male control 6 elderly female control 11 elderly male AD 4 elderly female AD	25.2 ± 0.59, 60 ± 1.31, 65.5 ± 2.2, 65.5 ± 2.3, 69.5 ± 4.4	PSG with or without airflow	15, DSM-III and neurological exam	Asymptomatic elderly males and those with AD show subclinical SDB	–	Validity of association is compromised by small and uneven sample size, and selection of paid healthy participants	No blinding; comparable treatment groups
Reynolds III et al. (1985)	USA, 23 healthy elderly into 3 groups 17 major depression 21 dementia with probable AD	49–85, 69.3 ± 5.6 for control, 69.6 ± 7.0 for depressed, 70.3 ± 7.9 for demented	In-lab PSG without oxygen saturation monitoring	DSM-III, MMSE	Sleep apnea was found in 42.9% of demented patients, 17.6% of depressives, 4.3% controls ($x^2 = 9.90$, $p < 0.01$) Significant association in women but not men, 42 elderly women showed $x^2 = 8.56$, $p < 0.01$ Severity of dementia correlates with apnea index	Age, gender, duration of illness, dementia scores, sleep architecture changes	Medical screening helps to remove confounders; multiinfarct dementia is excluded	Small sample size, 1 night PSG does not cover internight variability, REM/NREM difference not differentiated
Hoch et al. (1986)	USA, 139 elderly individuals with SDB, into 4 groups	49–85, 69.3 ± 5.4 for 56 controls, 70.8 ± 6.6 for 35 depressed, 71.5 ± 8.1 for 24 demented, and 72.2 ± 8.1 for 24 mixed depression and dementia	PSG	Blessed Dementia Rating Scale, 34 (41.7%)	SDB occurred in 41.7% of AD patients, 5.4% of controls, 11.4% of depressive subjects, and 16.7% of mixed symptoms ($p < 0.001$). AHI correlates with the severity of dementia, not only in the 34 AD patients but also the entire sample ($r = 0.57$, $p < 0.01$). AD patients show more NREM-predominant apnea	Health status, education level, illness duration	Expanded sample size from Reynolds III et al. (1985) and added a mixed group	1-night PSG without oxygen desaturation, no blinding, gender allocation (female > male)
Erkinjuntti et al. (1987)	Finland, 3 groups multi-infarct dementia ($n = 19$), AD ($n = 21$), and healthy controls ($n = 26$)	65.9 ± 2.3 for multiinfarct dementia, 67.7 ± 2.1 for AD, 71.9 ± 1.6 for health control	Estimation by static charge-sensitive bed	Clinical exam and questionnaire	OSA I 47.5% of demented patients ad 19.2% of controls ($p < 0.05$) Duration of SDB > 10% in 60% of demented patients and 15.4% of controls ($p < 0.001$)	Greater severity in multi-infarct dementia; a higher AHI in male than female patients Depression	SDB estimation has issues of specificity and sensitivity	No standard PSG; control group was older
Ancoli-Israel et al. (1991)	USA, 235 nursing home patients	83.5 for 152 women and 79.7 for 83 men	Portable sleep recording, AHI of 5	Mattis Dementia Rating Scale, 96% of patients	70% have SDB; all patients with severe sleep apnea are also severely demented			
Dealberto et al. (1996)	Nantes, France, 1389 subjects in the EVA study	60–70	Sleep questionnaire	8 neuropsy-chological tests	SDB is associated with lower scores (≤10th percentile) in tests requiring visual attention skills; OR = 2.14 for snoring and 1.88 for apnea in Trail Making Test, OR = 1.80 for snoring and 1.58 for apnea in Digit Symbol Substitution Test	Age, gender, education level, tobacco, alcohol, depression, number of medications	Validity of association is strong; sampling is limited to one community in western France	Sleep questionnaire without PSG may create bias

Table 1 (*Continued*)

Author	Country and samples	Age (y)	OSA: ascertainment of cases	AD: N of cases and diagnostic criteria	Results	Covariants	Comment on positive criteria	Comment on risk of bias
Foley et al. (2003)	US, Honolulu-Asia Aging Study of Sleep Apnea, 718 Japanese-American men	79–97, in 1999 and 2000	In-home overnight PSG with Compumedics PS-2 system	Cognitive abilities screening instrument	Incidence of SDB: >70%; severe OSA: 19%; no association between SDB and cognitive functioning (memory, concentration, attention)	Age, marital status, year of educated, medical history	SDB classification based on AHI of 5 and 30	Excluded mild dementia, those on CPAP or O_2 therapy, 27.2% are older than 85, Japanese American men only
Mathieu et al. (2008)	Canada, 28 patients (2 women) with OSA and 30 controls (4 women)	25–75, two age groups, >50 or ≤50	In-lab PSG	MMSE and neuropsychol-ogical testing	Both OSA and age contributes to cognitive dysfunction, without interactions of the two variables	Age	No additive effects of age and OSA	Age cutoff of 50 may not be absolute
Alchanatis et al. (2008)	Greece, 30 younger and 28 older OSA patients and their controls	Two age groups, ≥50 or <50	PSG	Attention-alertness tests	Older OSA patients show cognitive decline in comparison with their age-matched controls; this is not seen in young OSA patients	Brain hypoxia, sleep fragmentation, comorbidities are discussed	Age-dependent cognitive deterioration in OSA patients	Age cutoff of 50 may not be absolute but most likely show disease burden
Spira et al. (2008)	USA, 448 women in the study of osteoporotic fractures	82.8 ± 3.4	Home PSG	MMSE or trails B	OR = 1.4 (1.03–1.9) for all SDB indices vs MMSE decline; OR = 3.4 (1.4–8.1) for AHI ≥30, OR = 2.7 (1.1–6.6) for SaO_2 nadir <80%	APOE ε4 allele	Contributing osteoporosis is not clear	Women only
Rongve et al. (2010)	Bi-country, 151 western Norway residents and 420 participants without dementia from the Mayo Clinic Study of Aging	75.4 ± 7.8	Questionnaire, outpatient clinics	97; DSM-IV	Sleep disturbance was present in 71% of subjects with dementia and 55.7% of control participants ($p = 0.001$) OR = 3.0 (1.2–7.1) for any sleep disorder, 2.0 (0.7–5.1) for OSA	Depression, anxiety	No PSG evaluation	Comparable treatment groups–AD patient in Norway and control from Minnesota, USA
Sforza et al. (2010)	France, the SYNAPSE study of 827 subjects (58.5% women)	68 ± 1.8	Home sleep study with HypnoPTT	Neuropsychological tests	No strong relationship between objective cognitive scores, severity of SDB, and ESS. AHI was related to delayed recall ($r = -0.113$, $p = 0.001$) ad color Stroop test ($r = -0.097$, $p = 0.005$). ODI was related to more variables	Gender, BMI, diabetic status, HTN, education level, anxiety and depression scores, ESS, BP, self-reported sleep time	Large and homogeneous population in France, no comorbidity	Cognitive assessment may be short of sensitivity and domain specificity
Carlson et al. (2011)	USA, 112 North Carolina retirees (72 women and 40 men)	70–92	PSQI, ESS, 2 nights in-lab PSG and cerebral oximetry	MMSE, cognitive test battery	Cognitive function correlates with awake resting cerebral oxyhemoglobin saturation and the reduction during sleep; subjects with a rise of $rcSO_2$ during sleep performed better on the Logical Memory ($t = -2.2$, $p < 0.05$) and visual reproduction ($t = -2.3$, $p < 0.05$)	Education, occupation, race	Objective measures	Cerebral oxyhemoglobin saturation was measured during awake, not asleep

Table 1 (*Continued*)

Author	Country and samples	Age (y)	OSA: ascertainment of cases	AD: N of cases and diagnostic criteria	Results	Covariants	Comment on positive criteria	Comment on risk of bias
Kim et al. (2011)	South Korea, 30 MCI patients and 30 controls		PSG in a Center for sleep and chronobiology	Neuropsychological test battery	Impaired language function in MCI patients is related to poor sleep quality and more severe OSA	–	Addresses sleep quality, not specific for sleep apnea	Comparison of MCI patient with control for sleep quality
Guarnieri et al. (2012)	Italy, 431 consecutive patients enrolled in 10 neurological centers	76.0 ± 8.4 for 130 patients with SDB, and 75.9 ± 9.8 for 111 without	Berlin questionnaire, PSQI	DSM-IV-TR	Patients with vascular dementia show higher frequency of OSA. AD and MCI have the same frequency of any sleep disorders	Vascular dementia, LBD, PDD, FTD, MCI besides AD	204 AD patients compared with those with other types of dementia	SDB as one variable; insomnia (>50% incidence) might be a confounder
Ju et al. (2012)	South Korea, 63 elderly (26 women)	68.2 ± 4.8	PSG in sleep lab	Neuropsychological test battery	Both mild-moderate and severe OSA groups had worsened performance in delayed recall and errors on the trail-making test part B. The oxygen desaturation index and education level both contributed to the deficit in delayed recall		Strong evidence of association of severity of OSA with delayed recall and executive function in cognitively healthy elderly	Comparison of AHI ≥15 with control of AHI < 15
Kim et al. (2013)	South Korea, 503 individuals from the Korean Genome and Epidemiology Study (KoGES), 2011, 70.97% female	59.63 ± 7.48	1-night portable PSG with Embletta	N/A; MRI for white matter change	Significant association was identified between (a) presence of moderate to severe OSA in asymptomatic patients (10.5%); and (b) WMC (39.6% patients). OR for moderate-severe OSA with WMC: 2.08; CI 1.05–4.13	White matter change, hypertension	Strong association with vascular dementia, not specific for AD	Asymmetrical sex ratio; structural neuroimaging without fMRI

WMC, white matter change; OR, odds ratio; CI, 95% confidence interval.

Table 2
Cohort studies.

Author, year	Country and samples	Age (y)	Follow-up (y)	OSA: ascertainment of cases	AD: N of cases and diagnostic criteria	Results	Covariants	Positive criteria	Risk of bias
Foley et al. (1999)	US, 2905 participants in Honolulu-Asia Aging Study of dementia	71–93	3 years	Self-report of breathing pauses, daytime sleepiness, habitual snoring	72; DSM-III-R, cognitive ability screening instrument (CASI)	The rate of cognitive impairment was twice as high in those with EDS. Age 85+ has OR 4.79 (CI 3.28–7.00) or 4.10 (CI 2.76–6.09) after including morbidity; BMI < 20 has OR 2.32 (CI 1.76–3.05) or 2.28 (CI 1.73–3.02) after including morbidity; breathing pauses has OR 0.68 (CI 0.26–1.78) or 0.66 (CI 0.25–1.78) after including morbidity	Age, BMI, marital status, COPD and other medical problems	Strength of association is compromised by questionnaire only for sleep apnea	Selection bias – subjects chosen from positive answers from clinic; all Japanese-American men; possible carry-over not discussed
Cohen-Zion et al. (2001)	USA, 46 subjects	65 and older	2–8 years	Home PSG and sleep questionnaire	MMSE	Decreased cognitive performance is associated with RDI ($p = 0.036$) and daytime sleepiness ($p = 0.002$)	Age, education, oxygen saturation levels	Cognitive decline is associated with increased daytime sleepiness, but association with RDI is not strong	MMSE as the main cognitive parameter; concern of sensitivity and specificity
Cooke et al. (2009a)	USA, 5 with CPAP use and 5 discontinued use (3 women)	75.7 ± 5.9	13.3 ± 5.2 months	Home PSG, sleep questionnaire	Neuropsychological test battery	Less cognitive decline with sustained CPAP use	Sex, race, education	Subjects are not matched for gender, BMI, OSA severity, or basal cognitive function	Small size exploratory study, no blinding, more men than women
Canessa et al. (2011)	Italy, 17 with OSA and 15 controls	30–55	3 months	PSG, AHI > 30	Neuropsychologic evaluation, MRI with voxel-based morphometry	CPAP improved memory, attention, executive function, better preserved gray matter volume in hippocampus and frontal cortex	Extent of hypoxia	Presence of clinical data of treatment efficacy	Covariant analysis of basal cognitive function not shown
Yaffe et al. (2011)	USA, 298 women without dementia	82.3 ± 3.2	4.7 (3.2–6.2)	Home PSG with Siesta, 105 women (35.2%), AHI ≥15	MMSE, neuropsychological test battery, DSM IV, 60	MCI and dementia AOR = 1.85 (95% CI 1.11–3.08) for SDB vs no-SDB; MCI AOR 1.71 (1.04–2.83) and dementia AOR 2.04 (1.10–3.78) for desaturation index and %SDB time	Age, race, BMI, education, smoking, DM, HTN, stroke, depression, medication 7	SDB associated with cognitive decline; treatment intervention and duration of disease unclear	Women only
Chang et al. (2013)	Taiwan, 1414 patients with OSA and 7070 matched controls	40% in 40–49, 30.9% in 50–59, 15.5% in 60–69, 13.6% in ≥70; 59.3% male	5 year (4.78 ±1.11 for SA and 4.93 ± 0.61 for control)	Documented diagnosis of sleep apnea in database	Clinical diagnosis with ICD-9 codes	The development of dementia was more likely in the first 2.5 years of follow up. The adjusted HR was 1.7 overall and 2.38 for women. Males in the 50's had 6.08 times greater risk, whereas females at age 70 or older had 3.20 times greater risk of developing dementia	Urbanization levels, age, sex, index year, HTN, DM, hyperlipi-demia, stroke	Strong; Cox proportional hazard analysis with stratification; age and time depended risk factor analysis	Duration of SA not clear

RR: relative risk; HR: hazard ratios; OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval.

Table 3
Randomized double-blind placebo-controlled trials.

Author, year	Country and samples	Age (y)	Design	Duration of intervention	OSA: ascertainment of cases	AD: N of cases and diagnostic criteria	Results
Chong et al. (2006)	US, 39		Parallel group	6 weeks	PSG, AHI ≥ 10	39 AD patients	Therapeutic CPAP use decreased ESS after 3 weeks
Ancoli-Israel et al. (2008)	US, 52	77.8 ± 7.3	Parallel group	3–6 weeks	PSG, AHI ≥ 10	Neuropsychological testing	CPAP improved cognition in OSA patients treated with CPAP for 6 weeks or 3 weeks, mainly in episodic verbal learning and memory
Moraes et al. (2008)	Brazil, 11 OSA and 10 controls	62–87	Parallel group	3 months	2-nights in-lab PSG, AHI > 5	Probability criteria of the Alzheimer's Disease and Related Disorders Association; MMSE, ADAS-cog subscale, brain MRI, lab tests; 33 mild-to-moderate AD patients	Donepezil improved AHI, desaturation index, duration and extent of hypoxemia, suggesting that the cholinesterase inhibitor improves subjective measures of OSA. Independently, it also increased REM sleep duration and reduced ADAS-cog scores
Sukys-Claudino et al. (2012)	Brazil, 21, including 11 in donepezil and 10 in control treatment	35–65	Parallel group	2 months	In-lab PSGs, AHI > 10	No known AD	Donepazil reduces ESS scores but also decreases sleep efficiency

review. However, these disorders are also associated with sleep apnea as well as other aspects of sleep disorders. Cross-sectional studies analyzing multiple cognitive domains have great strength, and case controlled prospective cohort points to an increased incidence of cognitive decline in patients with sleep apnea (Chang et al., 2013). Since the incidence of OSA ranged from 33 to 70% among AD patients in different reports, if CPAP treatment partially rescues cognitive dysfunction, this will make a major impact on disease progression. New treatment studies, particularly double-blinded randomized trials, are necessary to fully establish a causal relational and eventually improve the standard of care.

There are several limitations to the existing data. (a) Most studies are cross-sectional surveys, with inconsistent findings among different studies. The totality of evidence needs to be further addressed. (b) Although the strength of association between severe OSA and cognitive decline is supported by large odds ratios, further dose-response studies may need to be stratified not only to the mild, moderate, and severe categories of OSA, but also to a combination of the duration of disease, extent of intermittent hypoxemia, severity of sleep fragmentation, and comorbidity. Co-variant analysis of small vessel ischemic disease will help to identify the contribution of obesity, diabetes, and hypertension that often co-exist with OSA. (c) The design and sample size of double-blinded, placebo controlled clinical trials to test the effect of CPAP need to be improved. Non-inferiority trials with sleep apnea dental devices or other non-PAP modalities will also be informative.

3. Imaging the sleepy brain

If OSA has a causal relationship leading to a subset of AD, one may be able to detect AD-specific neuropathology as a result of increased disease burden. For example, longer duration and more severe untreated OSA might be related to greater Aβ pathology, plaque formation, or brain atrophy. A relatively specific imaging biomarker is Aβ deposition in positron emission tomography (PET) studies. There are limitations; for example, the PET agent Pittsburg Compound B (PiB) binds to soluble fibrils instead of the pathogenic Aβ oligomers. The rate of amyloid deposition is slow and constant, whereas the rate of neurodegeneration late in life shows a greater correlation with magnetic resonance imaging (MRI) evidence of neuropathology dissociated from amyloid deposition (Jack Jr. et al., 2009). However, multimodality imaging is able to provide useful clues to show how OSA contributes to neurodegeneration. Region-specific changes of blood flow and metabolism contrast with typical AD without comorbid intermittent hypoxemia and metabolic disturbance.

There may be several implications of sleep brain imaging. First, sleep invokes different patterns of brain activation than waking states. This may be detected by use of surrogate markers, such as changes of CBF and metabolism, activation of immediate early genes, or changes of electrophysiological signals. Second, sleep manipulations, including restriction, deprivation, and extension, either targeting selective stages or the entire process, might alter functional connectivity in distinct brain regions in response to specific tasks. Third, sustained sleep disorders induce neuropathological changes, such as seen in sleep apnea, insomnia, and REM behavioral disorders. Structural changes may be apparent in addition to functional and neurochemical abnormalities.

Different modalities of neuroimaging address various aspects of normal sleep and neuropathology related to abnormal sleep. MRI measures neuroanatomical metrics such as cortical thickening on volumetric imaging. Functional MRI (fMRI) assesses a default mode network or activation in response to psychological trial blocks or other evocative stimuli, determines white matter integrity by use of diffusion tensor imaging, and is supported by pharmacological MRI (phMRI) after administration of agonists to specific subtype of receptor for neurotransmitters. Magnetic resonance spectroscopy (MRS) detects biochemical changes. PET and single photon emission tomography (SPECT) measures CBF and metabolism of glucose or classical neurotransmitters along with functional near infrared imaging (fNIR) and can be combined

with transcranial magnetic stimulation (TMS) and other approaches.

In combination with EEG recording and use of imaging analysis by statistical parametric mapping, PET imaging started an era of sleep imaging. This has provided essential information on sleep stage-associated changes of CBF and metabolism (Maquet et al., 1990; Maquet, 1999, 2000). However, PET imaging has the limitation of temporal resolution, and is difficult to use for analysis of brief sleep phenomena such as spindles or K-complexes. An EEG-fMRI combination has overcome some of the hurdles, but it is susceptible to physiological noise and scanner noise that need to be compensated (Kaufmann et al., 2006; Laufs et al., 2007).

Normally, NREM sleep results in reduced activity in multiple brain regions, whereas REM sleep is associated with increased activity in some areas with reduction in others. The default mode network connectivity remains and cortical activation can be present in light stages of NREM sleep, as seen with fMRI by an increased blood oxygen level dependent (BOLD) signal in visual cortex and primary sensory cortex (Horovitz et al., 2008). Sleep disruption results in cognitive deficits in modalities of vigilance and attention (Verstraeten et al., 2004), processing speed and mental flexibility (Naismith et al., 2004), and retrieval of information from semantic memory (Lee et al., 1999).

There are neuroimaging correlates of this. PET imaging of regional blood flow shows prefrontal and posterior parietal hypometabolism after sleep deprivation (Braun et al., 1997). PET imaging of glucose metabolism shows a decreased cerebral metabolic rate in the thalamus and prefrontal and posterior parietal cortices (Thomas et al., 2000). In a recent cross-sectional study of cognitively normal volunteers, excessive daytime sleepiness (high ESS scores) was associated with decreased functional connectivity in the default mode network. Age, sex, brain structure, or body mass index did not have an effect on this inverse correlation (Ward et al., 2013). In a recent PET imaging study with PIB in 76 subjects (53–91 years old) in Baltimore, Aβ burden was associated with self-reported sleep variables, and inversely correlated with sleep quality and sleep duration (Spira et al., 2013). At the least, there is a bidirectional relationship between sleep quality and Aβ load. Sleep fragmentation and behaviorally induced insufficient sleep syndrome are probably major contributors to the neuropathology besides sleep disordered breathing, as will be further discussed in Section 4 below.

High-resolution T1-weighted MRI was used to assess brain morphology in 21 OSA patients and 21 controls. Voxel-based morphometry showed that OSA patients had gray matter loss in multiple and often unilateral sites. These include frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum. The structural changes underlie the deterioration of upper airway motor control and cognitive function (Macey et al., 2002). Structural changes and functional activation patterns in OSA subjects show overlap with those in AD, but there is no exact match. In general, OSA appears to have greater impairment of the frontal lobe in both animal and human studies (Beebe and Gozal, 2002; Matthews and Aloia, 2011). Hypoxia induces subcortical lesions, and this might underlie the structural basis of irreversibility of psychomotor functioning despite PAP treatment (Matthews and Aloia, 2011). In regard to fMRI, there have been reports of both over- and underactivation of specific brain regions (Ayalon et al., 2009b). A lack of working memory task-related signal activity is seen in the dorsolateral prefrontal cortex (Thomas et al., 2005), and an increase of activation in response to attention tasks is also seen in several brain regions, indicating greater recruitment of compensatory resources (Ayalon et al., 2009a). In another study, working memory tasks evoked a greater increase of fMRI signal in the right parietal lobe but reduction in the cerebellar vermis in OSA patients than controls (Archbold et al., 2009). Reduction of prefrontal fMRI activation in performance of n-back working memory tasks occurs in OSA patients even without nocturnal hypoxia. There is also a decrease in the extent and the bilateral nature of posterior parietal activation. CPAP treatment does not improve the hyporeactivity despite a complete subjective clinical recovery (Thomas et al., 2005). This contrasts with the partial correction of working memory deficits when OSA patients are treated with CPAP (Naegele et al., 1998; Lee et al., 1999; Ferini-Strambi et al., 2003; Naismith et al., 2004; Santamaria et al., 2007; Sanchez et al., 2009). The discrepancy of recovery/reversibility of deficits may be dependent of the duration of treatment, as well as the sensitivity of tests reflecting different aspects of disease processes. The pattern of neuroimaging abnormality in OSA patients with cognitive decline contrasts with that of classical AD, which often shows early involvement of the temporal lobe and hippocampus (Reinvang et al., 2013).

There have not been longitudinal studies testing the null hypothesis that prolonged OSA does not correlate with increased Aβ deposition or AD-like neuroimaging changes. Nonetheless, concurrent PET and MRI analyses have been used to determine a predictive value of amyloid deposition and structural changes with cognitive decline (Jack Jr. et al., 2009; Frisoni et al., 2013). Areas susceptible to high levels of Aβ have been identified, such as the precuneus and posterior cingulated region of the default mode network shown by fMRI (Sperling et al., 2009). Activities in these areas are affected by sleep disturbance, raising the possibility of impaired Aβ clearance resulting from severe OSA.

OSA is related to metabolic and microstructural changes in brain regions, as shown by multivoxel MRS analysis. Severe OSA increases N-acetyl aspartate/creatine ratios in the hippocampus and choline/creatine ratios in both hippocampus and putamen. By contrast, N-acetyl aspartate/choline ratios in putamen were decreased in patients with severe OSA in comparison with mild OSA (Alkan et al., 2013). Collectively, the results suggest a reduction of energy metabolism and increased cellular turnover in neurons.

Overall, OSA impairs CBF in fMRI studies and metabolism in MRS and PET imaging, and alters brain activation patterns. There is overlap and dissimilarities with classical AD as described above. CPAP treatment does not provide a quick fix for fMRI hyporeactivity though working memory shows some recovery. It is essential that future functional imaging studies characterize differences of AD brains with and without OSA.

4. Sleep disruption and intermittent hypoxia alter Aβ processing and BBB clearance

AD is a protein aggregation disorder. Both sleep disruption and intermittent hypoxia, hallmarks of OSA, facilitate protein aggregation in animal and cellular models. Fig. 1 shows a tentative model of how these two factors could lead to neurodegeneration.

Defective processing of amyloid precursor protein (APP) is the best characterized mechanism of AD pathology. APP is processed by the enzymes beta-secretase (BACE1) and presenilin-1 (PS1)/gamma-secretase to generate Aβ. Sleep disturbance has been shown to precipitate brain Aβ in a mouse model of AD. In APP transgenic mice, chronic sleep restriction increases Aβ plaque formation. Even acute sleep deprivation is sufficient to increase the amount of interstitial Aβ recovered by microdialysis. The change is similar to that seen when mice are infused with orexin, a sleep promoting neuropeptide. On the contrary, infusion of a dual orexin receptor antagonist decreases Aβ level and reduces plaque formation (Kang et al., 2009).

Even in the absence of OSA, sleep quality shows some correlation with Aβ deposition. In a cross-sectional study involving 142 cognitively normal adults monitored by actigraphy, the estimated sleep efficiency was worse in a subgroup of patients (22.5%) who

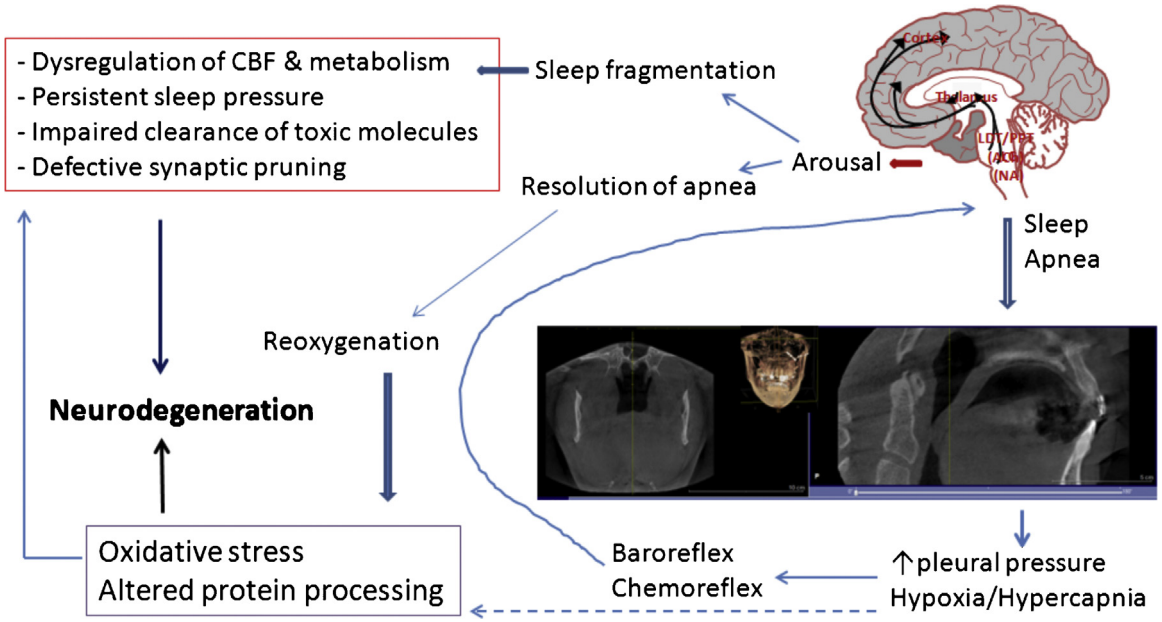

Fig. 1. A working model of how OSA results in neurodegeneration. The dental images of a patient with severe OSA show a coronal view of the oropharynx (left), and oblique mid-sagittal view of focal obstruction while awake in an upright inhaling position (right), which worsens during sleep (GALILEOS 3D digital X-ray software). As a result of structural and functional obstruction in the upper airway, sleep apnea increases pleural pressure, results in hypoxia and hypercapnia, with activation of baroreflexes and chemoreflexes. The afferent input through dorsal vagal and cranial nerves activates brainstem respiratory groups through the nucleus tractus solitarius and associated pathways. Modulation of respiratory patterns and cessation of apnea also induce cortical arousal, causing sleep fragmentation. The combined consequence of sleep fragmentation and oxidative stress alters cellular functions and CNS connectivity.

were CSF Aβ42-positive. Their poorer sleep efficiency also correlated with increased daytime napping (Ju et al., 2013). Poor sleep quality and impaired Aβ clearance have reciprocal interactions, although future sleep and AD research should also identify other biomarkers.

In OSA, intermittent hypoxia and oxidative stress are major contributors to tissue injury. There is abundant evidence that hypoxia promotes Aβ aggregation. Acute hypoxia induces hypoxia inducible factor (HIF)-1α and facilitates its binding to BACE1 promoter. This increases BACE1 mRNA and enzyme activity and leads to higher levels of Aβ and the APP C-terminal fragment-beta. This contrasts with the lack of effect of hypoxia on PS1, APP, and the TNFα-converting enzyme (TACE) that cleaves APP at the alpha-secretase cleavage site (Zhang et al., 2007).

The involvement of TACE entails the inflammatory aspect of OSA. TACE, also called ADAM17, is a member of the family of ADAM (a disintegrin and metalloproteinase) proteins that participate in the cleavage of membrane proteins, including TNF receptors and TNF itself. By increasing endoplasmic reticulum (ER) stress and the unfolded protein response, hypoxia activates ADAM17 and ectodomain shedding of TNFR1 through mitogen-activated protein kinases pathway and generation of reactive oxygen species (Rzymski et al., 2012).

OSA is an inflammatory process that leads to hyperleptinemia and increased proinflammatory cytokines in the circulation (Alberti et al., 2003; Pan and Kastin, 2014). Since sleep regulates both innate and acquired immunity, sleep disturbance and hypoxia further exacerbate neuroimmune dysfunction. Both OSA and an in vitro model of intermittent hypoxia delay the apoptosis of polymorphonuclear (PMN) leukocytes (neutrophils) and increase their expression of adhesion molecules. These PMNs have more opportunities to interact with vascular endothelia and result in greater damage by means of free radical and proteolytic enzyme release. In patients with moderately severe OSA (AHI higher than 15 events/h), PMNs have a lower level of caspase-3 and less nuclear condensation, indicating less apoptosis. While the severity of OSA correlates with more adhesion molecules and less apoptosis, CPAP treatment was effective in attenuating these changes (Dyugovskaya et al., 2008).

Even short-term exposure to intermittent hypoxia (3 days) is sufficient to increase HIF-1α, upregulate BACE that generates Aβ, and increase presenilin that regulates proteolytic events of γ-secretase leading to Aβ formation. Hippocampal Aβ can be reduced by melatonin in rats through BACE- but not presenilin-dependent mechanisms (Ng et al., 2010). In triple transgenic AD mice with 4 weeks of manipulation of oxygenation (5% O_2 and 21% O_2 every 10 min for 8 h/day), there is higher brain Aβ42 but not Aβ40, and greater intracellular Aβ, despite a lack of change of cognitive function. This alternating oxygen condition also facilitates Aβ42 secretion in a cultured neuroblastoma cell line overexpressing Aβ42 (Shiota et al., 2013).

Since hypoxia in mice leads to an increase of cerebral amyloid plaques and tau phosphorylation, it is suspected that analogous situations occur in patients with OSA and chronic intermittent hypoxia (Daulatzai, 2013). This might be a biochemical basis by which OSA results in AD-like pathology. In addition, dysfunction of the ER with protein misfolding is seen in many neurological disorders (Roussel et al., 2013). Energy failure and Aβ toxicity could collectively increase ER stress and AD-like pathology.

Certainly, the neuropathology is dependent on the chronicity of the insult and does not always involve Aβ processing. Rats exposed to chronic intermittent hypoxia show poorer performance in the Morris water maze, decreased hippocampal thioredoxin mRNA and protein levels, and apoptosis of hippocampal neurons (Yang et al., 2012). Transgenic mice expressing the human apolipoprotein E4 transgene show disrupted slow wave and REM sleep after intermittent hypoxia combined with sleep fragmentation. There is slower recovery from hypersomnolence afterwards (Kaushal et al., 2012).

After hypoxia, reoxygenation results in oxidative stress and damage to blood vessels and endothelial cells. Therefore, one would

predict a greater impact of OSA on blood–brain barrier (BBB) function and small vessels than on neurons in gray matter. Perhaps for this reason, it remains debatable whether OSA is more likely to induce AD or vascular dementia (Antonelli et al., 2004; Abrams, 2005; Roman, 2005). Nonetheless, OSA alters CBF and metabolism, as discussed in the preceding section on functional imaging.

Regulatory changes of the BBB and gliovascular coupling occur in sleep and anesthesia, and they contribute to Aβ clearance. In a recent 2-photon analysis in mice, natural sleep or anesthesia were associated with a 60% increase of interstitial space determined by tetramethylammonium diffusion. This accelerated convective exchange of cerebrospinal fluid with interstitial fluid facilitates Aβ clearance, suggesting that sleep helps to dissipate the build-up of neurotoxic waste products to achieve its restorative effect (Xie et al., 2013). This is consistent with the observation that APPswe/PS1δE9 mice show normal sleep-wake cycle and diurnal fluctuation in brain Aβ, but have deteriorated sleep and loss of the diurnal rhythm of Aβ in the interstitial fluid (Roh et al., 2012). The BBB participates in Aβ clearance (Pan et al., 2002; Banks et al., 2011) and mobilizes several transporters including lipoprotein-related protein and P-glycoprotein (Shibata et al., 2000; Cirrito et al., 2005; Hartz et al., 2010). Aging itself results in changes of BBB permeation of Aβ, its antibody, and presenilin 1 (Mackic et al., 2002; Banks et al., 2003; Kumar et al., 2009; Erickson and Banks, 2013). We recently showed that sleep deprivation decreases the expression of P-glycoprotein efflux transporter, glucose transporter, and several tight junction proteins. This is associated with decreased transport function and metabolic activity of the BBB microvessels (He et al., 2014). It appears that sleep activates the "detox system" in the CNS, thus helping to maintain cellular homeostasis, improve synaptic plasticity, and thereby contribute to memory consolidation and retention (Tononi and Cirelli, 2014). Overall, there is accumulating evidence that OSA impairs the homeostasis of protein folding and clearance through multiple mechanisms.

Astrocytes play crucial roles in regulating sleep pressure, reflected by the intensity of slow wave sleep. Adenosine and purinergic transmission are main features of astrocytes. In transgenic mice expressing inducible dominant negative SNARE protein in astrocytes, astrocytic release of adenosine is impaired. In these mice, sleep homeostasis is impaired either after sleep deprivation (Halassa et al., 2009) or lipopolysaccharide induced neuroinflammation (Nadjar et al., 2013). The important role of astrocytes in regulating sleep pressure is consistent with their function in glycogen storage and metabolic coupling (Petit et al., 2010). Reactive astrogliosis is seen in the brainstem of patients with sudden infant death syndrome (Sawaguchi et al., 2002, 2003), and in the hippocampus of rats 5 days after sleep deprivation, when nitric oxide synthase and nicotinamide adenine dinucleotide phosphate-diaphorase reactivity is inhibited (Hsu et al., 2003). Thus, an association of OSA with reactive astrogliosis is not surprising, and it is supported by a specific increase of serum S100β in OSA patients. The increase of astrocytic derived S100β contrasts with a lack of change in neuronal specific enolase (Braga et al., 2006). Region-specific reactive gliosis is present in animal models of obesity (Pan et al., 2008; Hsuchou et al., 2009; Pan et al., 2011, 2012) as well as obese people (Thaler et al., 2012). The consequence and impact of reactive astrogliosis in obesity and OSA are illustrated in Fig. 2.

Sleep fragmentation alone is sufficient to increase adenosine levels in hypothalamic homogenates from mice, and impair the circadian rhythm of autophagy protein expression in different CNS regions. Hypoxia and oxidative stress are stronger inducers of ER stress, protein misfolding, and altered autophagy. AD is associated with dysfunctions in both the ubiquitin–proteasome system and autophagy (Hook et al., 2008; Cecarini et al., 2012; Lee et al., 2013; Salminen et al., 2013). Many interactive proteins participate in the production,

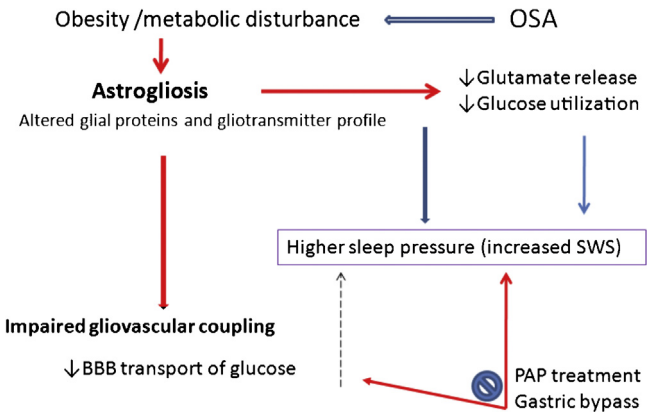

Fig. 2. Proposed key role of reactive astrogliosis in sleep disruption and BBB dysfunction. In OSA, both metabolic disturbance and oxidative stress lead to altered astrocytic activities and eventually results in reactive astrogliosis. This changes gliovascular coupling (interactions between astrocytes and the BBB) and metabolic coupling (neuron-glial interactions), with altered glucose and glutamate metabolism. Gliotransmitters, such as adenosine, are major contributors to sleep pressure, reflected by slow wave sleep (SWS). The gliosis may be partially alleviated by positive airway pressure (PAP) treatment or gastric bypass.

intracellular sorting, and proteolytic processing to ameliorate protein aggregation in the CNS (Haass et al., 2012). Certainly, the key regulators are not confined to Aβ, and dementia is not restricted to AD. If cellular assays identify a direct causal relationship from OSA-like pathology to protein aggregation within the CNS and impaired Aβ clearance across the BBB, this will provide a better basis for treatment an important subset of neurodegenerative disorders.

5. Overall summary and prospective

We reviewed clinical reports addressing association, interactions, and possible causal relationship between OSA and AD, and discussed confounding factors, strengths, and limitations of the existing trials (Tables 1–3). We then turned to sleep brain imaging to determine the overlap and dissimilarities of structural and functional activation in patients carrying these two diagnoses, and focused on the temporal and spatial patterns of Aβ deposition. Since Aβ aggregation remains the best established biomarker for AD, we examined the cellular results of how intermittent hypoxia and oxidative stress impair ER functions, disrupt autophagy, and interfere with protein processing. The roles of inflammatory mediators and reactive gliosis in the impairment of synaptic connectivity and neuronal functions were briefly discussed.

It should be pointed out that there is most probably a bidirectional relationship between SDB and cognitive decline. Besides AD-like changes, OSA might involve overlapping cognitive domains, and thus contribute to only a portion of patients with AD. Sleep fragmentation or sleep restriction alone may impair Aβ clearance and contribute to the neuropathology of dementia. Vascular dementia and synucleinopathies are also related to OSA and other sleep disorders. Placing the topic of review ("overlap syndrome" of OSA and AD) in the context of sleep disorders and neurodegeneration, long-term care and placement of the demented patients should take into consideration the normalization of sleep to preserve cognitive function. This includes treatment of SDB, parasomnia, insomnia, and circadian phase related sleep disorders.

To fully establish the link that OSA causes AD, future studies need to identify cellular mechanisms by which intermittent hypoxia and sleep disruption lead to protein aggregation disorders. At the level of cell biology and physiology, we need experiments on cell–cell interactions at the level of BBB (neurovascular

interface) and metabolic coupling between neurons and glia. This will be complementary to studies of brain connectivity and global network activation that are made possible by high resolution real-time imaging and electrophysiology to distinguish different sleep-waking states. Neurodegeneration studies should be carried out in animal models resembling OSA. Clinically, prospective cohorts and randomized treatment trials with sufficient statistical power are necessary to firmly establish a link between OSA and AD. In the meantime, there is no doubt that prolonged OSA leads to cognitive decline as well as systemic presentations. Therefore, prevention and treatment of OSA should be the responsibility of all physicians.

Search strategy and selection criteria

References for this Review were identified by searches of PubMed between 1969 and January, 2014, and references from relevant articles. The search terms "obstructive sleep apnea", "Alzheimer's disease", "Neurodegeneration", "Sleep disruption", and "Amyloid" were used. Section 2 mainly used the first two, for English language full papers. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Authors' contribution

Both WP (85% effort) and AJK (15% effort) performed literature search and wrote the review.

Conflict of interest

There is no conflict of interest from either author.

Acknowledgements

Research by AJK and WP are supported by NIH funding (DK54880, DK92245, NS62291). We thank Drs. Robert J. Thomas and Yi He for discussions.

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